REMARKS

The requisite fee for a three month extension of time can be charged to Deposit Account No. 02-1818. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 02-1818. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 02-1818.

Claims 8-14 and 58-73 are pending in this application. Claim 58 is amended for clarity.

THE REJECTION OF CLAIMS 8-14 AND 58-72 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

> Claims 8-14 and 58-72 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter. The Examiner urges that claim 58 allegedly provides multiple conflicting descriptions of the oligonucleotide family members encompassed by the instant claim because it is unclear whether the members must encode a transcription product that comprises a sequence that is complementary to mRNA that comprises the sample nucleic acid. The Examiner urges that dependent claim 59 similarly is unclear.

Reconsideration of the grounds for this rejection respectfully is requested in view of the amendments herein and the following remarks.

Claim 58 as amended recites in all instances the mRNA transcribed from the target nucleic acid molecule that "comprises the sample nucleic acid sequence in the target nucleic acid molecule." In addition, the claim recites that the oligonucleotide family members all include nucleic acid complementary to the sample. Therefore inhibition of expression by the oligonucleotide family is directly associated with the sample nucleic acid sequence in the target.

REJECTION OF CLAIMS 8-14 AND 58-73 UNDER 35 U.S.C. §103(a)

Claims 8-14 and 58-73 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wagner *et al.* U.S. Patent No. 6,355,415 and Draper *et al.* (U.S. Patent No. 5,496,698) in view of Gudkov *et al.* U.S. Patent No. 5,753,432. It is alleged that Wagner *et al.* teaches a method for assessing gene function in which ribozymes transiently or stably are transfected into a host cell, and the effect of ribozyme expression on the transfected cell and/or progeny derived from this cell is determined compared to controls that either are not transfected with the expression or are transfected with an expression vector that encodes an RNA that does not

cleave the substrate RNA. The Examiner states that Draper *et al.* U.S. Patent No. 5,496,698, (at col. 1-3 and 10):

> teaches identifying one or more members of a combinatorial ribozyme library by contacting mammalian cell culture with members of the library which bind to and disrupt a transcription product and identifying host cells that exhibit phenotypic changes, whereby members of the combinatorial library are identified; wherein the identified members are used as a probe to identify nucleotide sequences; and wherein the transcription product is mRNA. . . . Draper, at col. 2, lines 47-60, states: "[A]pplicant provides an in vivo system for selection of ribozymes targeted to a defined RNA target. The system allows many steps in a selection process for desired ribozymes to be bypassed. In this system, a population of ribozymes having different substrate binding arms (and thus active at different RNA sequences) is introduced into a population of cells including a target RNA molecule. The cells are designed such that only those cells including a useful ribozyme will provide a detectable signal. In this way, a large population of randomly or nonrandomly formed ribozyme molecules may be tested in an environment which is close to the true environment in which the ribozyme might be utilized as a therapeutic agent."

The Examiner states that Wagner *et al.* and Draper *et al.* do not teach that their methods do not comprise intervening bacterial cloning steps or that the method does not comprise conformational modeling of mRNA transcribed from the target nucleic acid molecule. The Examiner, however, urges that "the prior art discloses methods for assigning function to a transcription product of a target nucleic acid without the need for intervening bacterial cloning steps and conformational modeling" and cites Gudkov *et al.*, presumably for this proposition. The Examiner states that Gudkov *et al.* provides methods for designing a retroviral library of nucleic acid fragments to be delivered to eukaryotic cells to test or determine the ability of these nucleic acid fragments to function as genetic suppressor elements (GSE) (see col. 10-12). The methods of Gudkov *et al.* essentially comprise methods for identifying gene function since the ability of the putative nucleic acid molecules to function, as a GSE is unknown prior to testing. Moreover, the methods of Gudkov *et al.* do not recite intervening bacterial cloning steps or conformational modeling.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to have modified:

> the teachings of Wagner *et al.* and Draper *et al.* with the teachings of Gudkov *et al.* in the design of the instant invention. One of ordinary skill in the art would have been motivated to make this modification since Wagner *et al.* and Draper *et al.* expressly state that their disclosed methods for determining gene function encompass wherein the transfection method comprises the use of retroviral vectors and the teachings of Gudkov *et al.* are specifically designed to deliver nucleic acid to cells using retroviral vectors with the express purpose of determining their ability to alter a phenotype of the transfected cells.

This rejection respectfully is traversed. The Examiner states that the cited art is applied to the extent that the instant claims are interpreted as encompassing methods in which "gene function is assigned based upon the observation of "changes in the phenotype" of non-bacterial cells **expressing one or more members of an oligonucleotide family that function to inhibit the expression of an mRNA transcribed from a target nucleic acid sequence**, in comparison to the phenotype of cells not expressing one or more members of an oligonucleotide family. It appears that amendment of the claims to render it clear that the oligonucleotide family inhibits expression of the sample nucleic acid should obviate the rejection. Nevertheless, in order to be fully responsive, and also because such art does not render the claims as interpreted by the Examiner *prima facie* obvious.

Relevant Law

To establish prima facie obviousness under 35 U.S.C. §103, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). This principle of U.S. law regarding obviousness was not altered by the recent Supreme Court holding in KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 82 USPQ2d 1385 (2007). In KSR, the Supreme Court stated that "Section 103 forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1734, 82 USPQ2d 1385, 1391 (2007).

The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ2d 1780 (Fed. Cir. 1992); see, also, In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980).

The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). See also KSR, 127 S.Ct. at 1734, 82 USPQ2d at 1391 ("While the sequence of these questions might be reordered in any particular case, the [Graham] factors continue to define the inquiry that controls.") The Court

in Graham noted that evidence of secondary considerations, such as commercial success, long felt but unsolved needs, failure of others, etc., "might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." 383 U.S. at 18, 148 USPQ at 467. Furthermore, the Court in KSR took the opportunity to reiterate a second long-standing principle of U.S. law: that a holding of obviousness requires the fact finder (here, the Examiner), to make explicit the analysis supporting a rejection under 35 U.S.C. 103, stating that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. Id. at 1740-41, 82 USPQ2d at 1396 (citing In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S. Ct. at 1731. The Court indicated that there is no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* "Thus, in cases involving new compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." Takeda v. Alphapharm

THE CLAIMS

Independent Claim 58 is directed to high-throughput method of assigning a function associated with a product coded for by a sample nucleic acid sequence in a target nucleic acid molecule that includes by, **without any intervening bacterial cloning steps and without any conformational modeling of mRNA transcribed from the sample nucleic acid sequence in the target nucleic acid molecule:** a) delivering into, amplifying and expressing a plurality of members of an oligonucleotide family as individual transcription products in a plurality of recombinant non-bacterial host cells; and, b) in the resulting host cells, comparing the phenotypes of the resulting host cells to phenotypes of control cells to identify changes in phenotype to thereby assign a function associated with the product encoded by the sample nucleic acid sequence in the target nucleic acid molecule, wherein control cells are

untransfected host cells, whereby changes in phenotype can be assigned by comparison of the transfected host cell , and the un-transfected host cell. The oligonucleotide family comprises a plurality of nucleic acid molecules; each member of the oligonucleotide family encodes a transcription product comprising a sequence that is complementary to a sequence contained in the mRNA transcribed from the sample nucleic acid sequence in the target nucleic acid molecule;

the plurality of members of the oligonucleotide family are introduced into expression vectors, which are introduced into the host cells. The expression vectors contain double-stranded DNA, that contains: a) a sense strand and an antisense strand, wherein the sense strand encodes a transcription product that is complementary to and binds to an mRNA sequence transcribed from the sample nucleic acid sequence in the target nucleic molecule so that expression of a product coded for by the sample nucleic acid sequence is inhibited; and b) means for determining directionality of expression. The product encoded by the sample nucleic acid sequence is associated with at least one phenotypic property of a host cell containing the mRNA sequence; and the expression vector is for expression in non-bacterial host cells. The coding sequence for each individual transcription product encodes an antisense nucleic acid that binds to the mRNA transcribed from the sample nucleic acid sequence in the target nucleic acid molecule; and

expression of one or more of the individual transcription products inhibits production of a product of the mRNA.

Dependent claims further specify types of function, whether phenotypic change is monitored directly, types of sample nucleic acids, numbers of oligonucleotide family members, and types of high-throughput formats. Dependent claims 73 and 74 specify that the oligonucleotide family is a ribozyme family and claim 74 further specifies how the ribozyme oligonucleotide library is designed.

Differences Between the Claims and the Teachings of the Cited References

Wagner *et al.*

Wagner *et al.* is directed to the design of ribozymes that specifically cleave a target nucleic acid sequence of interest in a host cell, inhibit expression of a product encoded by the target nucleic acid and alter a phenotype in the host cell. The altered phenotype is then analyzed to identify the function of the product encoded by the target nucleic acid sequence of interest. Wagner *et al.* teaches that this method may be used to study genes that are homologous to mammalian, including human, genes in suitable model systems such as

zebrafish. The function of the homologous human or mammalian gene can then be deduced by identifying the function of the corresponding gene in zebrafish.

Wagner *et al.* teaches that the ribozymes targeting the nucleic acid sequence of interest **are designed by conformational modeling** of the secondary structure of the mRNA transcribed from the nucleic acid sequence of interest, identifying substrate cleavage sequences based on the observed secondary structure, then designing ribozymes directed to accessible cleavage sites in the mRNA (col. 17, line 63 to col. 19, line 14). Wagner *et al.* further states that the cleavage sequences may be located anywhere in the mRNA "so long as a ribozyme is capable of cleaving at or near the substrate cleavage site" (col. 19, lines 18-20). Wagner *et al.* further teaches that the binding regions of the ribozymes can be of any length "so long as the desirable specificity of the ribozyme for the RNA substrate and the desirable cleavage rate of the RNA substrate are achieved" (col. 20, lines 47-51). Wagner *et al.* exemplifies this method by demonstrating the computer modeling and identification of 3 accessible sites of mRNA transcribed from zebrafish *ntl* cDNA, then the design of 3 ribozymes that can cleave the 3 accessible sites and their use to identify the function of the *ntl* gene (*see* Example 1 beginning at col. 31).

Wagner *et al.* does not teach or suggest any high-throughput methods of assigning function to a product encoded by a target nucleic acid molecule by constructing an oligonucleotide family library based on complementary sequences throughout the mRNA transcribed from sample nucleic acid in the target molecule of interest. Wagner *et al.* does not teach or suggest constructing an oligonucleotide family library based on complementary sequences throughout the mRNA. Wagner *et al.* teaches the design of discrete ribozyme molecules directed against a target mRNA by studying the secondary structure of the mRNA for accessible sites. This is a time-consuming operation that is not amenable to a high throughput format. The instant method, on the other hand, avoids the step of assessing secondary structure for sites that are accessible to ribozyme cleavage or to antisense nucleotide binding. Instead, the oligonucleotide family is designed based on sequences that are complementary to sequences throughout the target mRNA. The plurality of oligonucleotide family molecules containing sequences so designed are then introduced into a plurality of host cells, expressed as individual transcription products in the host cells, and the host cells are assessed in high-throughput format for inhibition of expression of the target sequence of interest. Host cells that show inhibition of expression of the target are identified as containing oligonucleotide family members whose transcription products bind to the

mRNA molecule transcribed from the target nucleic acid molecule for whose product a function is assigned.

In the instantly claimed methods, the oligonucleotide family contains a plurality of putative antisense or ribozyme sequences, and the high-throughput method screens for the ones that effectively bind to and/or cleave the target mRNA. The oligonucleotide family is not designed based on a discrete selection of molecules that will effectively and/or selectively bind to and/or cleave the target mRNA. Rather, a large number of complementary sequences, regardless of whether their transcription products are effective antisense or ribozyme molecules, are used to make up the oligonucleotide family library.

Thus Wagner *et al.* is deficient in failing to teach or suggest virtually any elements of the instantly claimed method. For example, Wagner *et al.* fails to teach or suggest a high-throughput method of assigning a function associated with a product coded for encoded by a sample nucleic acid sequence in a target nucleic acid molecule; fails to teach or suggest a said method that does not include any intervening bacterial cloning steps and nor any conformational modeling of mRNA; and fails to teach or suggest a high throughput method.

Draper *et al.*

Draper *et al.* teaches a method for *in vivo* selection of a ribozyme active at a defined RNA target. According to Draper *et al.*, in the method a population of ribozymes having different substrate binding arms is introduced into a population of cells that express a target RNA molecule. The population of ribozymes contains ribozymes that differ in either or both ribozyme substrate binding arms whose sequence is randomized is "quasi-"randomized. Only cells that contain a ribozyme of desired specificity will survive or provide a detectable signal for selection of ribozymes of a desired specificity.

Hence Draper *et al.* provides a method for identifying ribozymes with a particular activity by screening a library of ribozymes with substrate binding arms that contain random or quasi-random sequences in order to produce and select ribozymes of a desired specificity. A library of ribozymes is introduced into cells and their activity is screened to identify ribozymes.

Draper *et al.*, does **not** provide a method for assigning a function to a gene product by inhibiting expression of the gene product using a family of oligonucleotides whose sequences are based on a sample sequence in a target. In the instantly claimed methods, the family of oligonucleotides, whose sequence is based on the target, is used, not to identify a particular ribozyme, but to permit inhibition of expression of a gene without the need to use

conformational modeling or to specifically design the oligonucleotides, in order to assign a function to the gene product.

Thus Draper *et al.* is of no relevance to the instantly claimed methods. Draper *et al.* does not teach or suggest any method of assigning function to a product encoded by a target nucleic acid molecule by constructing an oligonucleotide family library based on complementary sequences throughout the mRNA transcribed from sample nucleic acid in the target molecule of interest. Draper *et al.* does not teach or suggest constructing an oligonucleotide family library based on complementary sequences throughout the mRNA. Draper *et al.* does not teach or suggest a high throughput method. Further Draper *et al.* provides no teaching or suggestion that would have led one of ordinary skill in the art to have eliminated the conformational modeling in the method of Wagner *et al.*, nor does Draper *et al.* teach or suggest a high throughput method for assigning a function to a gene product that involves no bacterial cloning steps Thus, Draper *et al.* does not cure the deficiencies in the teaching of Wagner *et al.*

Gudkov *et al.*

Gudkov *et al.* is directed to the identification of genetic suppressor elements (GSEs). In the method of Gudkov *et al.*, **a random expression** library is constructed based on cDNA derived from normal cells. The random library is then screened for inserts that render cells immortalized, tumorigenic or morphologically transformed to identify GSEs. The identified GSEs may then be used to screen full length cDNA molecules and identify the corresponding genes.

Gudkov *et al.* does not teach or suggest any method of assigning a function to a product encoded by a known sequence of interest. Gudkov *et al.* identifies heretofore unknown sequences as being GSEs. Gudkov *et al.* does not teach or suggest use of or preparation of oligonucleotide family library based on complementary sequences throughout the mRNA transcribed from the target molecule of interest, nor does Gudkov *et al.* teach or suggest a high throughput method. As discussed, the instant claims are directed to a method of assigning a function to a known target gene of interest. The target sequence is known, but its function is unknown. The oligonucleotide family used in the instant method is designed based on this known target sequence (*i.e.*, identifying sequences that are complementary to the known target sequence). Gudkov *et al.*, however, employs a random library of all cDNA, known and unknown sequences, derived from a normal cell. Heretofore unknown (new) GSE sequences are then identified from this random library. This method is completely

different from the instant claimed method. Thus, Gudkov *et al.* does not cure the deficiencies in the teachings of Wagner *et al.* and Draper *et al.*

ANALYSIS

It respectfully is submitted that the Examiner has failed to set forth a case of *prima facie* obviousness. As discussed above, Wagner *et al.* teaches a method for assigning a function to a gene product, but does not does not teach or suggest a high-throughput method of assigning a function to a product encoded by a target nucleic acid of interest nor a method that does not involve intervening cloning steps. In Wagner *et al.*, ribozymes are designed by conformational modeling based on studying the secondary structure of the mRNA for accessible cleavage sites against the mRNA transcribed from a target nucleic acid are discretely identified as being effective at cleaving the mRNA. This is time-consuming and not amenable to a high-throughput screen. The oligonucleotide family library used in the instant high-throughput method, on the other hand, is based on complementary sequences throughout the target mRNA rather than assessing its secondary structure for accessible binding and/or cleavage sites.

Draper *et al.* provides a method for identifying and selecting ribozymes, not for assigning a gene function. There is no suggestion in Draper *et al.* for replacing the conformational modeling employed by Wagner *et al.*, for design of its ribozymes nor does Wagner *et al.* teach or suggest that its method of conformational modeling should be altered. In Draper *et al.* the method is for identification of ribozymes, not for assigning gene function, which is a very different purpose for which Wagner *et al.* models its ribozymes.

Gudkov *et al.*, which identifies <u>new</u> GSEs is not directed to a method of assigning function to a product encoded by a <u>known</u> sequence of interest, does not cure these deficiencies Gudkov *et al.* employs a random library of fragments derived from cDNA from normal cells, from which new GSEs are identified. Gudkov *et al.* does not appear to have any relevance to the instantly claimed methods. Gudkov *et al.* does not describe any method for assigning function to a transcription product of a target nucleic acid without the need for intervening bacterial cloning steps and conformational modeling.

The instant method screens a plurality of complementary sequences from an oligonucleotide family in a plurality of host cells, then identifies the family members that effectively bind to and/or cleave the target mRNA by identifying those host cells that show inhibition of expression of a product of the mRNA. This renders the method amenable to high-throughput format by avoiding the steps of conformational modeling of secondary

structures of the target mRNA and discrete design of ribozyme (or antisense) molecules directed against accessible sites.

There is no teaching or suggestion in either Wagner *et al.*. Draper *et al.*, or Gudkov *et al.*, singly or in any combination of a high throughput method for assigning a function to a product encoded by a known target sequence. The only reference that assesses gene function is that of Wagner *et al.*, but Wagner *et al.* fails to teach or suggest eliminating the conformational modeling steps nor eliminating any intervening bacterial cloning steps. Its method **relies** upon conformational modeling to design its ribozymes. Draper *et al.* is directed to a screening method for identifying and selecting ribozymes. Its method is not combinable with that of Wagner *et al.* Further, neither Wagner *et al.* nor Draper *et al.* provide a suggestion for eliminating the conformational modeling and intervening bacterial cloning steps employed by Wagner. As discussed above, the mere fact that prior art may be modified to produce that which is claim does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ2d 1780 (Fed. Cir. 1992); see, also, In re Papesch, 315 F.2d 381, 137 USPQ. 43 (CCPA 1963). There is nothing in the cited are that suggests eliminating the conformational modeling step, upon which the method of Wagner *et al.* relies.

Gudkov *et al.* does not cure these deficiencies. Gudkov *et al.* teaches identification of heretofore unknown sequences possessing a certain property (GSE) from a random cDNA library. Thus, the combination of teachings of the cited references does not result in the instantly claimed method.

None of the cited references, singly or in any combinations, teaches or suggests a high throughput method for assigning a gene function nor elimination of any intervening bacterial cloning steps, nor changing the Wagner *et al.* method to eliminate the conformational modeling. Therefore, the examiner has failed to set forth a *prima facie* case of obviousness.

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In view of the above amendments and remarks, reconsideration and allowance of the application respectfully are requested.

Respectfully submitted,

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